

Application No.: 10/585,916

Docket No.: 415852001100

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(PATENT)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Patent Application of:  
Michelle L. STYLES et al.

Application No.: 10/585,916

Confirmation No.:

Filed: January 12, 2005 (Int'l)

Art Unit: 1624

For: SELECTIVE KINASE INHIBITORS

Examiner: Douglas M. Willis

**DECLARATION OF CHRISTOPHER JOHN BURNS UNDER 37 C.F.R. § 1.132**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Dear Sir:

I, Christopher John Burns, declare as follows:

1. I am one of the co-inventors of the above-referenced application, and am familiar with the contents thereof.
2. I am the Research Director at Cytopia Research Pty Ltd, which is the owner of the present application. I am experienced in and remain actively engaged in the field of pharmaceutical research and development, particularly in medicinal chemistry and rational drug design. A copy of my *curriculum vitae* is attached hereto as Exhibit A.
3. Along with my colleagues, I undertook experiments to develop an optimized compound which would selectively inhibit the JAK3 enzyme. A pivotal part of these experiments was analysis of predicted binding mode of compounds to the JAK3 enzyme by in silico screening of

compounds, and verifying compounds activity using in vitro enzyme analysis. Experimental results for exemplary compounds of the invention are set forth below in the paragraphs that follow.

4. During discussions with my colleagues, a hypothesis was made that highly specific inhibitors of the JAK3 enzyme could be made by designing a moiety to interact irreversibly with the Cysteine residue in the putative ATP binding site of the JAK3 enzyme. It was considered that residues with the functionality known to chemists as a "Michael acceptor" could be capable of such irreversible binding.

5. It is known to me based on my experience as a synthetic and medicinal chemist that for a compound to function in a Michael reaction as an acceptor it need generally possess  $\alpha,\beta$  unsaturation such that the Michael donor can react with the  $\beta$  carbon atom. Examples of moieties known to me to function as Michael acceptors, and moieties which do not have this function capability, are attached hereto as Exhibit B.

6. Exemplary compounds of the invention, and other comparator compounds, were tested by my colleagues in an in vitro enzyme assay to determine the levels of inhibition of various enzymes, including JAK2 and JAK3.

7. The results of the tests are attached hereto as Exhibit C. The results of the enzyme assays are expressed as an IC50 of inhibition in  $\mu\text{M}$ .

8. Referring to Exhibit C, it is noted that compounds 1 and 2 are identical except for the moiety on the far right hand side, which in the case of compound 1 is known to me to be a Michael acceptor, and in the case of compound 2 is known to me not to be a Michael acceptor. . There is notably a greater than 10 FOLD difference in activity between compound 1 and compound 2 against the JAK3 enzyme, with the compound containing the Michael acceptor demonstrating much greater activity. Similarly it is noted that compounds 3, 4 and 5 are identical with except for the moiety on the far right hand side, which in the case of compounds 3 and 4 are known to me to be Michael acceptors, and in the case of compound 5 is known to me not to be a Michael acceptor. . There is notably a greater than 10 FOLD difference in activity between compounds 3 and 4 compared with

compound 5 against the JAK3 enzyme, with the compounds containing the Michael acceptor again demonstrating much greater activity.

9. These data are clear evidence in support of the hypothesis that including a moiety which is a Michael acceptor within a compound, in specific positions in the compound, greatly increases its ability to inhibit the JAK3 enzyme.

10. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Executed at Melbourne, VIC, Australia, on 14, Jan 2010.  
(city, state, country) (day, month)

Christopher Burns  
[insert name]  
